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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,976	05/23/2001	Farzan Rastinejad	PC10228B	1819

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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,976	RASTINEJAD ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-56* is/are pending in the application.

4a) Of the above claim(s) *56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-45,47 and 54* is/are rejected.

7)☒ Claim(s) *46,48-53 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/23/01;5/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The following is responsive to Applicant's election received Jan. 26, 2004.

Claims 1-25 are cancelled. Claims 26-56 are currently pending.

Applicant's election of Group I with a further election of spectroscopy, without traverse is acknowledged. Claim 56 is withdrawn from consideration.

The Examiner's requirement for election of a species of organic non-peptide compound is withdrawn in view of Applicant's remarks.

Information Disclosure Statement(s)

Applicant's Information Disclosure Statements have been considered in part. Please refer to Applicant's copies of the 1449's submitted herewith. The references listed on the 1449's were not found in the parent file. Furthermore, please note that the abstract submitted with the IDS of June 18, 2001 did not appear as a legible abstract when scanned. A legible copy is respectfully requested.

Specification

The Examiner respectfully requests that the following changes be made to the "**Brief Description of the Drawings**":

At page 10, line 27, "Figure 1" should be deleted and replaced with –Figures 1A-C--.

At page 11, line 1, "Figure 2" should be deleted and replaced with –Figures 2A-C--.

At page 11, line 11, "Figure 3" should be deleted and replaced with –Figures 3A-B--.

The attempt to incorporate subject matter into this application by reference to hyperlinks (please see page 13, line 34 and page 36, line 29) is improper because hyperlinks and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § 608.01(p).

Claim Objection(s)

1. Claims 26, 55 are objected to because of the following informalities: In claim 26, lines 2-3, the phrase ",whether mutant or wild-type," should be deleted and at line 2, before "mammalian", the phrase –mutant or wild-type—should be added. In claim 55, line 2, an –s—should be added to the end of the verb "promote". Appropriate correction is required.

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 52-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of **mAb 1620 or mAb 240** is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species **mAb 1620 or mAb 240**. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. ' 112, first paragraph. See, 37 C.F.R. 1.801-1.809. In evaluating the facts of the instant case, the following is noted:

It is apparent that the **mAb 1620 or mAb 240** is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of

the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 28, 38, 41, 42, 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 28 recites the limitation "measurement of said conformation" in line 1. There is insufficient antecedent basis for this limitation in the claim.

5. Claim 38 recites the limitation "the ... measuring steps" in line 1. There is insufficient antecedent basis for this limitation in the claim.

6. Claim 41 recites the limitation "said screening" in line 1. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 42 recites the limitation "the measurement" in line 1. There is insufficient antecedent basis for this limitation in the claim.

8. Claim 43 recites the limitation "the test compound" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejection(s)—35 USC 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 26, 28-31, 36-37, 42, 54 are rejected under 35 U.S.C. 102(e) as being anticipated by Welch et al., 5,900,360.

Welch et al. disclose a method of improving phenotypic defects that are caused by conformationally defective target proteins by contacting the protein with a protein stabilizing agent. Specifically, Welch et al. teach a method of correcting mutant p53 proteins with chemical chaperones. A rat cell line expressing a temperature sensitive mutant p53 protein having a missense mutation was used to study the effects of the protein stabilizing agents. The cells are contacted with protein stabilizing agents such as methylamine, but other agents such amino acids, polymers (polyethylene glycol), erythritol, inositol or trehalose are also readily envisaged. The cells and stabilizing agent are incubated for several days at 39.5^{O} C. Welch et al. then determined from the results that the stabilizing agents bound to the mutant p53 protein and restored the protein's wild-type conformation. The protein stabilizing agents are capable of stabilizing a protein in a biologically active conformation. It also acts to stabilize proteins under conditions that can cause denaturation or aggregation. Moreover, the protein stabilizing agents are easier to obtain chemically and are more stable and easier to administer than protein chaperones. The disclosed stabilizing agents are readily taken up by a cell. Finally, Welch et al. teach that these agents, or "chemical chaperones", are effective in the treatment of diseases, which involve defective protein folding and/or a failure in normal protein trafficking and maturation events, i.e. p53 (cancer). Please see the abstract; col. 3, lines 40-57; col. 4, lines 15-30; col. 5, line 25 to col. 6, line 2; col. 7, lines 15-65; col. 8, lines 55-57; Example 3.

The Examiner notes in Applicant's specification at page 15, lines 26-32 that the invention excludes from its scope the use of stabilizing agents such as glycerol, trimethylamine oxide and deuterated water. However, the Examiner respectfully submits that this statement is not commensurate in scope with the claims. That is to say that the claims as amended provide for no such exclusion.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 27, 28, 32-33, 34, 35, 38-41, 44-45, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welch et al., supra in view of Das et al.

Welch et al. as applied above.

Welch et al. do not disclose determining stabilized or functional conformation using spectroscopy. However, the Examiner refers to the Das et al., which disclose the use of fluorescence spectroscopy to determine the conformation of a destabilized protein bound to the chaperone α-crystallin, which is known to suppress the aggregation of damaged proteins. Please see the abstract.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Welch et al. by using spectroscopy to determine the stabilized or functional conformation of the mutant p53 protein bound to the stabilizing agents because one of ordinary skill in the art would reasonably expect spectroscopy to be equally effective in studying the interaction between the mutant p53 protein and stabilizing agent of Welch et al. Such a modification would have been motivated by the reasonable expectation of determining the conformational aspects of the bound mutant protein and agent thereby accurately identifying the non-peptide compound that may be useful in treating cancer.

Concerning the claims drawn to the use of a human p53 protein and the use of various mutant proteins (claim 32-34), one of ordinary skill in the art would reasonably expect these specific types of mutant p53 proteins as well as a p53 protein from a

human to be equally useful in the claimed identification method, especially since the identified non-peptide compounds may be eventually useful in treating cancer in humans.

With respect to claims 39-41, additional screening of the identified compound for anti-tumor activity using cell lines or tumor cells is an art-recognized, result-effective variable and it would have been obvious to one of ordinary skill in the art to modify it in the method of Welch et al.

Finally, the use of antibodies as a linking agent to a solid support as well as the use of radioisotope or fluorescent labels are conventional and well within the capability of the skilled artisan.

Claims 46, 48-53, 55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 26-45, 47, 54 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cybille Delacroix-Muirheid whose telephone number is 571-272-0572. The examiner can normally be reached on Mon-Fri from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached at 571-272-0584. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM

May 29, 2004

Cybille Delacroix-Muirheid
Patent Examiner Group 1600